Table 1
Formulations Used in Excipient Compatibility Study

No	Test Excipient (%)	Other Ingredients (%)
F1	Control	Avicel PH 112 (77), Explotab (8), Syloid (0.25), Mg Stearate (0.25)
F2	Talc (0.25)	Avicel PH 112 (77), Explotab (8), Mg Stearate (0.25)
F3	Stearic Acid (1)	Avicel PH 112 (76), Explotab (8), Syloid (0.25)
F4	Crospovidone (5)	Avicel PH 112 (80), Syloid (0.25), Mg Stearate (0.25)
F5	Nu-Tab (77)	Explotab (8), Syloid (0.25), Mg. Stearate (0.25)
F6	Avicel PH 112 (38.6), Nu-Tab (38.6)	Explotab (8), Syloid (0.25), Mg. Stearate (0.25)
F7	Nu-Tab (39.9), Crospovidone (5)	Avicel PH 112 (39.9), Syloid (0.25), Mg. Stearate (0.25)
F8	Nu-Tab (40), Crospovidone (5), no Syloid	Avicel PH 112 (40), Mg. Stearate (0.5)

Table 2

Formulations Investigated to Select Anti-Oxidant

No.	Antioxidant (%)	Other Excipient	Tablet Wt (mg)
W1	None	Crospovidone	200
W2	Methionine (0.5)	Crospovidone	20
W3	Ascorbic Acid (1)	Crospovidone	200
W4	Methionine (0.5)	None	250
W5	Methionine (0.5) (EDTA) (0.8)	None	250

Table 3
rhIL-11 Leading Tablet Formulation
Manufactured by Fluid Bed Granulation

Ingredients	**mg / tablet**
Intragranular	
rhIL-11 (concentrate equivalent to 2.5 mg)	5.561
Avicel PH 102	92.50
Na_2HPO_4 Anhydrous	8.50
NaH_2PO_4 Anhydrous	6.50
Methionine	1.00
Tween 80	0.339
Extragranular	
Avicel PH 112	73.5
Na_2HPO_4 Anhydrous	4.25
NaH_2PO_4 Anhydrous	3.25
Explotab	4.00
Magnesium Stearate	0.60
Total	200
Coating	
Eudragit L30D	5%

Table 4
Effect of Physical Stress on the Integrity of rhIL-11

Hardness (Kp)	Recovery[a] (%)	Multimer[b] (%)	Met 58 (%)	Related (%)
2.4	111.0	0.2	4.1	3.7
4.0	105.3	0.3	4.2	3.9
7.5	96.4	0.3	4.4	4.1
12.8	100.2	0.2	4.3	4.0

[a] Measured by RP-HPLC [b] measured by Size Exclusion Chromatography.

Table 5

In Vitro Bio-activity by T-10 bioassay

(Directly compressed tablets of rhIL-11)

Formulation	Sp Act Uwho/mg	IC Sp Act Uwho/mg
Tablet: Crospovidone, Syloid, Avicel, Mg Stearate	5.82E+06	6.70E+06
Blend: Avicel, Nu-Tab, Explotab, Syloid, Mg Stearate	6.57E+06	5.80E+06
Tablet: Avicel, Nu-Tab, Explotab, Syloid, Mg Stearate	6.38E+06	7.70E+06

Sp Act: Specific Activity; IC Sp Act: Internal Control Specific Activity

Table 6
Stability of Enteric Coated Tablets of rhIL-11
(by Fluid Bed Granulation)

Time (Weeks) (Conditions)	Strength (%)	Met[58] (%)	Related Species (%)
Initial	93.6	5.0	6.7
2 (40°C/75%RH)	86.9	4.5	3.4
4 (40°C/75%RH)	86.6	5.0	3.8
15 (Room Temp.)	94.1	4.0	4.9

Table 7: Sustained Release Tablet Formulations Prepared by Direct Compression

Ingredients	Formulation 1 (%)	Formulation 2 (%)	Formulation 3 (%)
Lyophilized rhIL-11*	6.3	6.0	5.7
HPMC (Methocel K4M PREM)	10.5	15	19
Microcrystalline Cellulose (Avicel PH112)	10.5	10	9.5
Sucrose (NU-TAB®)	68.5	65	62
Silicon Dioxide (Syloid)	0.26	0.25	0.24
Mg-stearate	0.79	0.75	0.71
Na_2HPO_4 (Anhydrous)	1.78	1.7	1.62
NaH_2PO_4 (Anhydrous)	1.37	1.3	1.24

* Each tablet contains 2.5 mg rhIL-11.

Table 8: Composition of Sustained Release Tablet Formulations Prepared by High Sheer Wet Granulation

Ingredients	Formulation 4 (%)	Formulation 5 (%)
rhIL-11*	1.0	1.0
Methocel K4M PREM	10.0	15.0
Avicel PH112	30.0	30.0
NU-TAB®	55.04	50.04
Syloid	0.25	0.25
Mg-stearate	0.74	0.74
Na_2HPO_4 (Anhydrous)	1.68	1.68
NaH_2PO_4 (Anhydrous)	1.29	1.29

* Each tablet contains 2.5 mg rhIL-11 added as bulk solution.

Table 9: Composition of Sustained Release Tablet Formulations Prepared by Fluid Bed Granulation Using Higher Viscosity Grades of HPMC

Ingredients	Formulation 6 (%)	Formulation 7 (%)	Formulation 8 (%)
rhIL-11 Granules*	48.6	45.7	45.7
Methocel K4M PREM	31.9	25	24
Methocel K15M PREM	-----	5.3	6.0
Mannitol	18.44	23.0	15.3
Avicel PH102	-----	-----	8.0
Syloid	0.26	0.25	0.25
Mg-Stearate	0.8	0.75	0.75

* Prepared by fluid bed granulation. Equivalent to 2.5 mg rhIL-11 per tablet.

Table 10: Composition of Sustained Release Tablet Formulations Prepared by Fluid Bed Granulation Using Lower Viscosity Grades of HPMC and Various Phosphate Buffer Species

Ingredients	Formulation 9 (%)	Formulation 10 (%)	Formulation 11 (%)	Formulation 12 (%)
rhIL-11 Granules*	45.7	45.7	45.7	45.7
Methocel K100 LV, LH, CR, Premium	25.0	30.0	25	25
Mannitol	16.3	------	-----	28.3
Syloid	0.25	0.25	0.25	0.25
Mg-Stearate	0.75	0.75	0.75	0.75
Na_2HPO_4	6.8	13.3	-----	-----
NaH_2PO_4	5.2	10	-----	-----
$(NH4)_2HPO_4$	-----	-----	16.1	-----
$(NH4)H_2PO_4$	-----	-----	12.2	-----

*Prepared by fluid bed granulation. Equivalent to 2.5 mg rhIL-11

Table 11: Composition of IL-11 Delayed Release Multiparticulate Capsules

Component	Percentage (% wt/wt)	Target for 5 mg Capsul (mg)
rhIL-11	1.10 [b]	5.500
Sugar spheres, NF	68.0	339.9
Glycine, USP	2.47	12.38
Sodium phosphate (dibasic), USP	0.180	0.8855
Sodium phosphate (monobasic), USP	0.060	0.3037
Polysorbate-80, NF	0.028	0.1377
Methionine, USP	0.206	1.028
Hydroxypropyl methylcellulose, USP	3.91	19.57
Methacrylic acid copolymer dispersion, NF (Eudragit L30D-55)	15.0	74.95
Talc, USP	7.50	37.49
Sodium hydroxide, NF	0.090	0.4496
Triethyl citrate, NF	1.50	7.490
Purified water, USP	Removed during processing	q.s.
Size #0 Hard gelatin capsule		
Total		500 mg

A 10% overage rhIL-11 is used to compensate for losses during manufacture.

Label/Package

Table 12 rhIL-11 Delayed Release Capsules, 5 mg/Capsule Long Term Storage at 2-8°C, 0-18 Months

Tests	Strength	Total Inactive Species	Met[58] – Oxidized Species	Impurities & rhIL-11 Related Species	Specific Activity (T-10 Bioassay)	Dissolution - Acid Stage (0.1 N HCl)	Dissolution Buffer Stage (Phosphate Buffer)	Moisture
						Average	Average	
Initial	4.60	9.4 %	6.7 %	2.7 %	8.1×10^6	3 %	76 %	1.1 %
1 Month	4.94	7.1 %	4.5 %	2.7 %	NS[b]	3 %	74 %	1.3 %
83 Days	4.94	6.3 %	4.0 %	2.3 %	7.0×10^6	3 %	82 %	1.1 %
6 Months	4.74	7.3 %	4.4 %	3.0 %	7.0×10^6	2 %	84 %	1.1 %
9 Months	5.02	8.1 %	5.3 %	2.8 %	1.1×10^7	3 %	65 %	2.4 %
12 Months	4.49	5.0 %	3.2 %	1.9 %	8.9×10^6	NT	NT	1.6 %
18 Months	4.60	5.8 %	4.0 %	1.8 %	8.0×10^6	1 %	69 %	1.1 %

Table 13 rhIL-11 Delayed Release Capsules, 5 mg/Capsule Long Term Storage at 25°C, 0-18 Months

Tests	Strength	Total Inactive Species	Met[58] – Oxidized Species	Impurities & rhIL-11 Related Species	Specific Activity (T-10 Bioassay)	Dissolution - Acid Stage (0.1 N HCl)	Dissolution Buffer Stage (Phosphate Buffer)	Moisture
						Average	Average	
Initial	4.60	9.4 %	6.7 %	2.7 %	8.1×10^6	3 %	76 %	1.1 %
1 Month	4.86	7.3 %	4.6 %	2.7 %	NS[b]	2 %	76 %	1.4 %
83 Days	4.82	6.6 %	4.0 %	2.5 %	6.9×10^6	3 %	80 %	1.2 %
6 Months	4.75	9.1 %	5.4 %	3.7 %	5.7×10^6	1 %	75 %	1.2 %
9 Months	4.87	10.3 %	6.7 %	3.6 %	1.2×10^7	2 %	65 %	1.5 %
12 Months	4.48	7.9 %	5.1 %	2.9 %	7.4×10^6	2 %	68 %	2.1 %